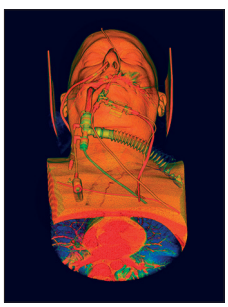
Advancing towards precision medicine in ARDS



K H Fung/Science Photo Library

Lancet Respir Med 2018

Published **Online**
April 12, 2018
http://dx.doi.org/10.1016/S2213-2600(18)30156-5

For the **study by Calfee and colleagues** see **Articles**
Lancet Respir Med 2014; **2:** 611–20

For more on the **stability of ARDS phenotypes over time** see *Thorax* 2018; published Feb 24. DOI:10.1136/thoraxjnl-2017-211090

For the **study by Famous and colleagues** see *Am J Respir Crit Care Med* 2017; **195:** 331–38

For the **study by Proudfoot and colleagues** see *Thorax* 2018; published Jan 29. DOI:10.1136/thoraxjnl-2017-210305

Acute respiratory distress syndrome (ARDS) is a complex clinical condition in which pulmonary oedema—often secondary to pneumonia, sepsis, or trauma—leads to acute-onset hypoxaemia and respiratory failure. Globally, ARDS accounts for 10% of all intensive care unit admissions, and hospital mortality from ARDS ranges from 35% to 46% depending on severity. Numerous clinical trials have been done since ARDS was described in 1967, yet no pharmacological therapies have been found that improve outcomes for patients with ARDS; treatment is restricted to supportive care with mechanical ventilation as the cornerstone. However, recent trends in ARDS research suggest that a precision medicine approach that individualises treatment for subgroups of patients with ARDS might play an important part in therapeutic efficacy in the future.

In 2014, Carolyn Calfee and colleagues published an analysis of the baseline clinical and plasma biomarker data from patients with ARDS who had participated in two randomised controlled trials (the ARMA study and the ALVEOLI study). Data from these two ARDS cohorts were assessed independently by latent class analysis to identify subgroups of patients with similar clinical and biological variables. In both cohorts, the authors identified two ARDS subgroups: a hyperinflammatory phenotype characterised by higher levels of inflammatory biomarkers, shock, metabolic acidosis, and mortality, and a second, non-hyperinflammatory phenotype. Furthermore, the two phenotypes had differential responses to treatment; when the effect of high versus low positive end-expiratory pressures (PEEP) on mortality was assessed by phenotype in the ALVEOLI cohort, the hyperinflammatory subphenotype was more responsive to high PEEP whereas the non-hyperinflammatory phenotype was more responsive to low PEEP. Importantly, in a condition that can progress rapidly over the course of hours, the two ARDS phenotypes remained predominantly stable over the three-day period.

Investigating ARDS phenotypes in a third cohort, Katie Famous and colleagues used latent class analysis to reanalyse baseline clinical and biomarker data from 1000 patients with ARDS in the randomised controlled trial Fluid and Catheter Treatment Trial (FACTT). The hyperinflammatory and non-hyperinflammatory phenotypes were identified in this cohort as well, with differential responses to fluid management strategies. When treatment responses were compared by phenotype, a fluid-conservative management strategy was associated with decreased mortality for the hyperinflammatory phenotype but with increased mortality for the non-hyperinflammatory phenotype. The investigators showed that a combination of three variables—interleukin-8, serum bicarbonate, and tumor necrosis factor receptor-1 (TNFR1)—could accurately identify ARDS phenotype in all three cohorts.

The role of phenotypes in the development of effective pharmacological therapies and in individualising treatment for patients with ARDS has yet to be fully elucidated. Calfee commented that the two biggest hurdles that need to be overcome in order to translate the phenotype findings into patient care are, "step 1: we need to be able to classify patients into subphenotypes in real-time or use point-of-care assays for measuring biomarkers that are critical for differentiating these two groups. There is not a commercially available assay to do this at present. Step 2: validating these findings prospectively."

Developing and individualising pharmacological therapies for the prevention of ARDS in high-risk patients are also in the early stages. Results from a study by Alastair Proudfoot and colleagues suggested that the inflammation and lung injury that precede ARDS might be reduced by GSK1995057, a first-in-class, nebulised, antibody fragment that specifically blocks TNFR1. In a laboratory model of lung inflammation, GSK1995057 pretreatment reduced TNFR1-mediated neutrophil influx and deleterious neutrophil-endothelial interactions; in a non-human primate model of acute lung injury, GSK1995057 pretreatment reduced pulmonary neutrophil influx and inflammatory markers. Furthermore, in a double-blind, randomised, placebo-controlled phase 1 trial (also part of the study by Proudfoot and colleagues) 37 healthy volunteers received a dose of nebulised GSK1995057 prior to endotoxin inhalation, the latter of which induced a transient, self-limiting irritation in the lungs as a model of lung injury in humans. GSK1995057 pretreatment in humans reduced pulmonary neutrophil influx and also reduced pulmonary and systemic markers of inflammation.

Senior author Daniel McAuley said of the study, "TNF is a master mediator of a lot of inflammation. GSK1995057 blocks one receptor [TNFR1] for TNF. In preclinical studies, when we pretreated with GSK1995057 we got significant reduction in the amount of inflammation in the lung. In a human model of lung injury, we pretreated with GSK1995057 and found reduction in inflammation. Therefore, GSK1995057 might have a role in prevention or treatment of ARDS." McAuley added that phase 2 studies with these types of drugs are being planned to target critically ill patients with potentially treatable traits.

Regarding the future of precision medicine in ARDS, McAuley said, "point-of-care testing is going to be key; a whole raft of work is being done in this area. Subgroups are being identified and point-of-care technology is coming along. These will make precision medicine possible in the critically ill." Calfee commented, "we're in very early days in this field—we have to be cautious and take it one step at a time, and recognise the limits of our understanding."

Judith A Gilbert